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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application: Hiroyuki Asada et al.

U.S.Patent Application Number: 10/526,822 Group Art Unit:1612

Filed: March 4, 2005 Examiner: Zohreh A. Fay

For: CLEAR OPHTHALMIC SOLUTION COMPRISING LATANOPROST AS ACTIVE INGREDIENT

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231
Sir:

I, Hiroyuki Asada, a citizen of Japan, hereby declare and state:

1. I am a joint inventor in the above identified application, and am a Japanese citizen, residing Nara-shi, Nara 631-0074 Japan.

2. I have been employed by Santen CO., LTD., Japan, the assignee of record in the present application. Since 1994, I have been engaged in that corporation and have had a total of 15 years of work and research experience in pharmaceutical development.

3. I am very familiar with the present invention, the above-identified application, the Office Actions dated on July 25, 2008 and the reference cited therein.

4. I and/or those under my direct supervision and control carried out comparative experiments to obtain data of appearance observation of ophthalmic solutions. I would like to report the results of the comparative tests below.

(1) Experiments A-1 and A-2

Description of Procedure for Experiments

Comparative formulations A-1 and A-2 were prepared as follows.

Purified water (approximately 90 ml) was placed in a 100 ml-glass beaker. Crystalline sodium dihydrogenphosphate (0.2 g) and sodium chloride (0.9 g) were dissolved in the purified water, pH was adjusted to 6.7 with a 1 N aqueous sodium hydroxide solution, and purified water was added to the mixture so that total volume was 100 ml to give a vehicle. The vehicle (100 ml) was added to latanoprost (5 mg), and the mixture was stirred while warming it in a water bath at about 80℃ to dissolve latanoprost in the vehicle. The temperature of the solution was returned to room temperature, and then pH was confirmed to be 6.7. Water for injection was added to the solution to adjust total volume to 100 ml. In a glass test tube was placed precisely 10 ml of the latanoprost solution, 70 or 30 μl of a 1% BAK (a mixture of compounds having 12, 14 and 16 carbon atoms of alkyl R in the above chemical structural formula) solution was added thereto, and they were mixed. These formulations are

shown in Table A.

Appearance of each solution prepared by the above-mentioned method was observed.

Table A also shows results of appearance observation of comparative formulations A-1 and A-2 together with the results of appearance observation of comparative formulations 3 and 4 obtained in Experiment 1 of the present specification.

Table A

	Comparative formulation A-1	Comparative formulation A-2	Comparative formulation 3	Comparative formulation 4
Latanoprost	0.005	0.005	0.005	0.005
Crystalline sodium dihydrogenphosphate	0.2	0.2	0.2	0.2
Sodium chloride	0.9	0.9	0.9	0.9
BAK	0.007	0.003	0.01	0.005
Diluted hydrochloric acid	q.s.	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.
Appearance	White turbidity	Slightly white turbidity	White turbidity	White turbidity

(Unit in Table: % (W/V), q.s.: quantum sufficient)

Analysis of Results

As obvious from Table A, not only in comparative formulations 3 and 4 containing 0.01% or 0.005 % of BAK but also in comparative formulations A-1 and A-2 containing 0.007 or 0.003% of BAK, white turbidity was observed.

(2) Experiments B-1 and B-2

Description of Procedure for Experiments

Formulations B-1 and B-2 were prepared as follows.

Purified water (approximately 90 ml) was placed in a 100 ml-glass beaker. Crystalline sodium dihydrogenphosphate (0.2 g) and sodium chloride (0.9 g) were dissolved in the purified water, pH was adjusted to 6.7 with a 1 N aqueous sodium hydroxide solution, and purified water was added to the mixture so that total volume was 100 ml to give a vehicle. The vehicle (100 ml) was added to latanoprost (5 mg), and the mixture was stirred while warming it in a water bath at about 80℃ to dissolve latanoprost in the vehicle. The temperature of the solution was returned to room temperature, and then pH was confirmed to be 6.7. Water for injection was added to the solution to adjust total volume to 100 ml. In a glass test tube was placed precisely 10 ml of the latanoprost solution, 70 or 30 μl of a 1% BAK-C_{12} solution was added thereto, and they were mixed. These formulations are shown in Table B.

Appearance of each solution prepared by the above-mentioned method was observed.

Table B also shows results of appearance observation of formulations B-1 and B 2 together with the results of appearance observation of formulations 3 and 4 obtained in Experiment 1 of the present specification.

Table B

	Formulation B-1	Formulation B-2	Formulation 4	Formulation 5
Latanoprost	0.005	0.005	0.005	0.005
Crystalline sodium dihydrogenphosphate	0.2	0.2	0.2	0.2
Sodium chloride	0.9	0.9	0.9	0.9
BAK C_{12}	0.007	0.003	0.01	0.005
Diluted hydrochloric acid	q.s.	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.
Appearance	Colorless and transparent	Colorless and transparent	Colorless and transparent	Colorless and transparent

(Unit in Table: % (W/V), q.s.: quantum sufficient)

Analysis of Results

As obvious from Table B, not only in formulations 4 and 5 containing 0.01% or 0.005 % of BAK-C_{12} instead of of BAK but also in formulations B-1 and B-2 containing 0.007 or 0.003% of BAK-C_{12} instead of BAK, white turbidity was not observed.

(3) Experiments C-1 to C-5

Description of Procedure for Experiments

Formulations C-1 to C-5 were prepared as follows.

Purified water (approximately 90 ml) was placed in a 100 ml-glass beaker. Crystalline sodium dihydrogenphosphate (0.2 g) and each nonionic tonicity agent were dissolved in the purified water so that each concentration was the value shown in Table C, pH was adjusted to 6.7 with an aqueous sodium hydroxide solution or diluted hydrochloric acid, and purified water was added to the mixture so that total volume was 100 ml to give a vehicle. The vehicle (100 ml) was added to latanoprost (5 mg), and the mixture was stirred while warming it in a water bath at about 80℃ to dissolve latanoprost in the vehicle. The temperature of the solution was returned to room temperature, and then pH was confirmed to be 6.7. Water for injection was added to the solution to adjust total volume to 100 ml. Into a glass test tube was placed precisely 10 ml of the latanoprost solution, 70 µl of a 1% BAK (a mixture of compounds having 12, 14 and 16 carbon atoms of alkyl R in the above chemical structural formula) solution was

added thereto, and they were mixed. These formulations are shown in Table C.

Appearance of each solution prepared by the above-mentioned method was observed.

Table C also shows results of appearance observation of formulations C-1 to C-5.

Table 4 shows the formulations 6 to 10 in Experiment 1 of the present specification and the results of appearance observation thereof.

Table C

	Formulation C-1	Formulation C-2	Formulation C-3	Formulation C-4	Formulation C-5
Latanoprost	0.005	0.005	0.005	0.005	0.005
Crystalline sodium dihydrogenphosphate	0.2	0.2	0.2	0.2	0.2
BAK	0.007	0.007	0.007	0.007	0.007
Concentrated glycerin	2.5	—	—	—	—
Mannitol	—	5	—	—	—
PEG 400	—	—	8.5	—	—
Propylene glycol	—	—	—	2.1	—
Trehalose	—	—	—	—	9.25
Diluted hydrochloric acid	q.s.	q.s.	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Appearance	Colorless and transparent	Colorless and transparent	Almost colorless transparent	Colorless and transparent	Colorless and transparent

(Unit in Table: % (W/V), q.s.: quantum sufficient)

Table 4

	Formulation 6	Formulation 7	Formulation 8	Formulation 9	Formulation 10
Latanoprost	0.005	0.005	0.005	0.005	0.005
Crystalline sodium dihydrogenphosphate	0.2	0.2	0.2	0.2	0.2
BAK	0.01	0.01	0.01	0.01	0.01
Concentrated glycerin	2.5	—	—	—	—
Mannitol	—	5	—	—	—
PEG 400	—	—	8.5	—	—
Propylene glycol	—	—	—	2.1	—
Trehalose	—	—	—	—	9.25
Diluted hydrochloric acid	q.s.	q.s.	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Appearance	Colorless and transparent	Colorless and transparent	Colorless and transparent	Colorless and transparent	Colorless and transparent

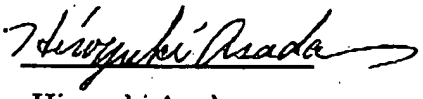
(Unit in Table: % (W/V), q.s.: quantum sufficient)

Analysis of Results

As obvious from Table C and Table 4, not only in formulations 6 to 10 containing 0.01% of BAK and the nonionic tonicity agent instead of sodium chloride but also formulations C-1 to C-5 containing 0.007% of BAK and the nonionic tonicity agent, white turbidity was not observed.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 20th day of January, 2009



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